Erectile dysfunction: diagnostic and therapeutic approach

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Abstract

Male sexual behavior is regulated by the combined action of several hormones, the most important of which is testosterone (T). GnRH and LH play a key role in regulating sexual desire and potency, but their importance in contributing to the pathophysiology of male impotence is still unclear. Psychoneuroendocrine causes of erectile dysfunction are related to stress altered secretion and/or function of the major central neurotransmitters (i.e. epinephrine, norephinephrine, opioid peptides, serotonin, dopamine, oxytocin) involved in the psychogenic regulation of erection. Studies of these alterations, which account for most of *non organic* causes of erectile dysfunction (about 50% out of the total causes of impotence), may be evaluated by the psychological profile (i.e. State Trait Anxiety Inventory) as well as by the measurement of biological (Bio) LH levels and of Bio/Immuno LH ratio. *Organic* factors account for the remaining causes of impotence and can be ruled out through an accurate evaluation of vascular, neurologic and endocrine function. Endocrine alterations (which represents about one third out of the organic causes) are evaluated by the assay of plasma total (T) and free testosterone (FT), estradiol (E), dehydrotestosterone (DHT), prolactin (PRL), thyrotropin-stimulating-hormone (TSH) and sex-hormone-binding-globulin (SHBG). The application of different diagnostic procedures and current therapeutic approaches is reviewed.

Introduction

Before the studies of Master/Johnson (1966), the sexual potency was considered as an expression of psychological mechanisms neither completely defined nor identified at the organic level. Except for the most common endocrine pathologies (diabetes and hypogonadism), it was considered that 80% of male erectile failure was to be blamed to psychogenic causes. Master/Johnson demonstrated that male sexual arousal is a true organic function, considered as an expression of vascular, neurologic and hormonal integrations like other organic functions (i.e.

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renal and hepatic). Extensive investigations were conducted on the CNS pathways controlling the erectile function and the identification of complex mechanisms which integrate / supervise this organic function. Male sexual function involves the neuroendocrine / vascular interactions and with psychological / social factors. Each of these factors is able to influence by itself the male sexual performance.

In USA some ten million males are affected by erectile dysfunctions (Furlow 1985). Erectile failure is an age-dependent disorder which affects 1% of the male population at > 49 years of age and 25% of men > 65 years of age (Krane et al, 1989). In certain groups of patients (i.e. diabetics and haemodialysated) there is a significant increase of this percentage (up to 90%) (Menchini Fabris et al, 1988). In the last few years the number of patients consulting the specialist for erectile disorders has increased enormously. The reason for this phenomenon is the growing social and medical sensitivity towards these problems. The real increase in the incidence of the pathologies which cause impotence is due to several factors: metabolic and vascular diseases, increase in alcohol and drugs consumption, cigarette smoking, stress in the life style, psychological changes in male social role.

I. Mechanism of erection

When the penis is flaccid, the corporeal smooth muscle is in a tonically contracted state, largely under sympathetic modulation (basal blood flow = 8 ml / min / 100 g tissue) (Wagner 1981). There are four crucial physiologic requirements for penile rigidity: intact neuronal innervation, intact arterial supply, appropriately responsive corporeal smooth muscle, and intact venous mechanic (Melman et al, 1993). Penile erections are elicited by local sensorial stimulations of the genital organs *(reflexogenic erections)* and by central psychogenic stimuli received form or generated within the brain *(psychogenic erections)*. Reflexogenic erections are mediated by a spinal reflex pathway in which the afferent limb consists of sensorial receptors located in the penile skin and glans that reach the dorsal nerve of the penis that in turn joins the pudendal nerve to reach the sacral spinal cord.

The efferent limb arises in the sacral parasympathetic centers and contributes fibers to the pelvic nerve, which enters the erectile tissue as the cavernosal nerve. The pathways for psychogenic erections are elicited by several stimuli (visual, auditory, gustatory, imaginative and tactile) that are integrated in different areas of the brain (i.e. thalamic nuclei, the rhinencephalon, the limbic structures and the medial preoptic-anterior hypothalamic area). These are projected to the sympathetic thoracolumbar and parasympathetic sacral tracts, where they join the penis through the pudendal nerve (Krane et al, 1989). Given an adequate hormonal milieu and appropriately responsive corpora, a rigid erection requires an increase of fivefold to tenfold in penile arterial inflow obtained through the release of several putative endogenous vasodilators: acetylcholine, prostaglandin-E1, Vasoactive-Intestinal-Polypeptide (VIP), Calcitonin-Gene-Related-Peptide and nitric oxideno. These vasodilators provoke smooth muscle relaxation.

The final requirement for a complete rigidity is the occlusion of venous outflow, determined from the high pressure exerted by the relaxed / enlarged trabecular walls that are forced against the tunica albuginea and that cause a subsequent venocclusion (Table 1). After

Table 1: Physiology of male sexual behavior (modified by Benson 1988)

PHASE	MECHANISM
I. FLACCID	Minimal variation of the inflow and outflow caused by the elevated resistance of the penile arterioles and the contraction of the smooth muscle tissue.
II. LATENCY	Increase of the hematic inflow in the internal pudendal arteries. The intracavernous pressure does not vary for at least 10 sec.
III. TUMESCENCE	Relaxation of the trabecular smooth muscle (through the local release of nitric oxide) expands the lacunar spaces causing the blood to fill up the penis. The intracavernous pressure increases while the hematic flow in the internal pudendal arteries decreases causing penile expansion and elongation.
IV. FULL ERECTION	Maximal turgidity is obtained. The hematic pressure expands the relaxed trabecular walls against the tunica albuginea, causing the further elongation of the penis with a subsequent compression of the subtunical venules that causes a reduction of the outflow from the lacunar space. The elevation of the pressure inside the lacunar spaces causes the penis to be rigid. The intracavernous pressure reaches up to 80-90% of the systolic pressure. Inflow is low but always remains superior to that of the flaccid phase. This phase needs a constant balance between inflow and outflow.
V. ORGASM	Resulting in sperm emission and ejaculation. Emission is controlled by the lumbar portion of the spinal sympathetic pathway, while ejaculation is provoked by contractions of the bulbocavernous muscles (mediated by the pudendal nerves) and is controlled by the voluntary motor system of the urethra and by the not-voluntary reflexes mediated by the α-1 post-synaptic adrenergic receptors. With the stimulation of sacral sympathetic pathway, norepinephrine (NE) is released in the intersynaptic space where it stimulates α-1 adrenergic post-synaptic receptors that are situated on the smooth muscle cell membrane; NE stimulates in turn the α-2 pre-synaptic adrenergic receptors that inhibit the release of NE from the assonic terminal (Clark et al, 1985). Afterwards, NE is degraded and inactivated by the monoamino-oxidases (MAO) and the catechol-o-methyl-transpherase (COMT).
VI. RESOLUTION	Detumescence is the result of the contraction of the smooth penile musculature caused by the activation of the sympathetic constrictory nerves (through the release of NE and other putative vasoconstrictors, i.e. endothelin and angiotensin II). This determines a decrease of arterial inflow, a collapse of the lacunar spaces with an increase of outflow and the return of the penile flaccidity.

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ejaculation, a local discharge of putative endogenous vasoconstrictors (i.e. epinephrine, norepinephrine, endotelin, angiotensin II) occurs in the penis. This is associated with a reduction of arterial flow, a collapse of lacunar spaces with a reduction of the pressure exerted against the thin venules of the tunica albugiena and a subsequent facilitation of venous outflow (Melman et al, 1993).

II. Pathophysiology

The causes of male sexual impotence are divided into organic and psychogenic causes (Table 2).

A. Psychogenic causes:

Psychogenic stimuli (frequently associated with anxiety) cause smooth muscle contraction of the corpora cavernosa through an increase of systemic (Hengeveld 1983) and intracavernous cathecolamines level (Melman, Henry 1979; Kim, Oh 1993) thus inhibiting reflexogenic erections. In impotent patients undergoing diagnostic intracavernous injection (ICI) of vasoactive drugs, there is a high level of anxiety, suggesting a possible role of anxiety in the etiology of erectile dysfunction (Aversa et al, 1995).

B. Organic causes:

1. Endocrine mechanisms

The regulation of male sexual behavior is determined by the combined action of several hormones, the most important of which is testosterone (T). GnRH and LH may regulate sexual desire and performance (Fabbri et al, 1988). Notwithstanding that T is clearly implicated in the development of sexual secondary characters and in the regulation of male sexual behavior. The mechanism by which it affects the pathophysiology of erection is still unclear. A direct link may be possible between the androgenic action and the central nervous regulation of erection. The neurovascular mechanisms that control erection operate even in the presence of low androgen levels (Canale et al, 1990). Penile erection is locally mediated by the release from human vascular endothelium of nitric oxide (NO) (Kim et al, 1991). DHT may be the active androgen in the prevention of erectile failure observed in castrated rats. This effect may be mediated, in part, by changes in NO-synthase levels in the penis, suggesting a possible action of this hormone in regulating NO-dependent erectile pathway (Lugg et al, 1995).

Hyperprolactinemia may cause a loss of libido / erectile failure. An inhibition of GnRH and LH secretion causes a subsequent reduction of T circulating levels. However, the androgen replacement therapy is not associated with a normalization of erectile function, suggesting that PRL may exert an antagonistic action to the peripheral action of testosterone (Rocco et al, 1990).

Thyroid dysfunctions may cause erectile disorders through unclear mechanisms. In patients with thyrotoxicosis, serum levels of T are often elevated. FT levels may be normal due to an elevated level of circulating SHBG in these subjects, or to a decreased response of Leydig

Table 2: Etiopathogenesis of male sexual impotence

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1. PSYCHOGENIC
- Anxiety
- Stress

2. ORGANIC

a. *Endocrine*
- Primary hypogonadism
- Secondary hypogonadism
- Hyperprolactinemia
- Dysthyroidism
- Adrenal disorders
- Diabetes
- Increased opioid levels (Stress?)

b. *Neurogenic*
- Central hereditary or acquired neuropathies
- Peripheral neuropathies
- Spinal cord injuries

c. *Vascular*
- Decreased inflow (arterial dysplasia, atherosclerosis, trauma, compressions)
- Increased outflow (venous leakage, insufficient smooth muscle cells relaxation)

d. *Iatrogenic*
- Anti-hypertensive agents ($\alpha-$ and $\beta-$blockers, sympatholythics)
- Vasodilators (i.e. hydralazine)
- Diuretics (i.e. thyazides)
- Anti-H2 (i.e. cymetidine)
- Centrally active drugs (i.e. triciclic antidepressants, neuroleptics, etc.)

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cell to LH-hCG. Hypothyroidism is associated with sexual dysfunction: T levels may decrease due to decreased circulating SHBG levels, whereas in contrast FT levels may be normal and PRL may be elevated (Benson 1993).

Stress may impair secretion of central neurotransmitters: serotonin, which inhibits sexual function through the stimulation of Corticotropin-Releasing-Hormone secretion; endogenous opioids which inhibit GnRH pulsatility; dopamine which stimulates the secretion from oxytocinergic hypothalamic neurons. Dysfunctional alterations in the pathways which regulate male sexual behavior lead to erectile failure (Fabbri et al, 1988). In these cases, medical treatment may be helpful: with antiserotonergic (i.e. trazodone; Saenz de Tejada et al, 1991) or central opiate receptor blockers (i.e. naltrexone; Fabbri et al, 1989) or dopamine agonists (i.e. apomorphine; Lal et al, 1987).

2. Neurogenic Mechanisms:

Every central (i.e. hereditary neuropathies) or peripheral disease (i.e. diabetes, chronic renal insufficiency, carcinoma, plasma cell dyscrasias, autoimmuno diseases, immunohaematologic disorders, AIDS, toxic neuropathies) affects the nervous terminal conduction to the penis, leading to erectile dysfunction. These alterations may affect the authonomic nervous system and may be provoked by acute or chronic diseases (i.e. Guillain-Barré syndrome and diabetic autonomic neuropathy, respectively). Erectile dysfunctions occur after spinal cord injuries, inguinal / gastrointestinal surgery and multiple sclerosis (Berger et al, 1993).

3. Vascular Mechanisms:

These are the most common organic causes of male sexual dysfunctions. Any kind of pathology which reduces cavernosal-hypogastric hematic flow decreases the perfusion pressure in the cavernous lacunar spaces, resulting in erectile failure (i.e. arterial dysplasia, Leriche's syndrome, hypertension and atherosclerosis) (Sharlip 1992). Several factors cause the dysfunction of the venoocclusive mechanism:

a) degeneration of sinusoidal smooth muscle, preventing sufficient expansion and compression of subtunical venules

b) the presence or development of large venous channels through the corpora cavernosa, which may result in excessive blood drainage with loss of erection

c) degeneration or trauma of the tunica albuginea, resulting in inadequate compression of the subtunical / emissary veins

d) insufficient or inadequate parasympathetic neurotransmitter release, which result in poor sinusoidal relaxation and failure of the venoocclusive mechanism, as will excessive sympathetic tone and

e) acquired venous shunts, which are the result of operative correction of priapism or Peyronie's disease (Lue, Donatucci 1993).

4. Iatrogenic Mechanisms:

Alcohol, tobacco, cannabis and other illegal drugs are associated with erectile

dysfunction. Several therapeutic agents can induce impotence through partially explained mechanisms. Sexual dysfunction is evident during anti-hypertensive therapy: α-methyldopa, clonidine, guanethidine, propranolol, prazosin and diuretics. These agents reduce libido, induce impotence and alter the ejaculation time (Bansal 1988). Calcium-antagonists (verapamil) may cause impotence through the inhibition of gonadotropins secretion (King et al, 1983). Psychoactive drugs may provoke impotence / ejaculation disturbances through the interference with cholinergic / adrenergic neurotransmission. Tricyclic antidepressants, which block central muscarinic / α-adrenergic receptors, may lead to retrograde / painful ejaculation by opposing the effect of parasympathetic / sympathetic nervous system (De Leo, Magni 1983). Neuroleptic drugs (phenothyazines, butyrophenones) are parasympatholytic, sympatholytic and may increase PRL serum levels by blocking the central dopaminergic receptors, inducing sexual dysfunctions (Falaschi et al, 1982). Anti-H2 histaminic receptor drugs may provoke gynaecomastia, galactorroea and impotence (Peden et al, 1970). Antiandrogens (cyproterone acetate, spironolactone, flutamide, ketoconazole) are involved in the etiology of erectile dysfunctions (Rocco, Fabbrini 1989)

III. Diagnosis

An accurate medical history is important to identify risk factors and associated diseases (cigarette smoking, dyslipidemia, alcoholism, hypertension, diabetes mellitus, hyperprolactinemia, cerebral and myocardial infraction, neurologic diseases, pelvic traumas or surgery, stress, drugs). A detailed sexual history should include: acute or progressive onset of impotence, alterations of libido, presence of nocturnal and/or early morning related erections, presence of spontaneous erections, frequency of masturbation, ejaculatory disturbances and sexual couple satisfaction (Table 3).

1. Physical examination:

This examination should include special reference to presence of congenital or acquired bends of the penis (Peyronie's disease), testicular size and sensitivity, presence of gynaecomastia and/or galactorrhoea, body habitus, blood pressure and peripheric pulses.

2. Hormonal evaluation:

In order to rule out pituitary dysfunctions, a profile of gonadotropins (GT and PRL plasma levels (at 0, +15 and +30 min) should be performed for all impotent patients. A single plasma assay is not sufficient due to their pulsatile secretion. Low T and low GT levels indicate hypogonadotropic hypogonadism while low T and elevated GT levels indicate hypergonadotropic hypogonadism.

Low T levels are detected during hyperprolactinemia. If Bio/Immuno LH ratio is inferior to 3.5, a central dysregulation of the GnRH hypotalamic pulsatile secretion is suspected (Fabbri et al, 1988). FT plasma levels, often reduced in presence of high levels of circulating Sex-Hormone-Binding-Globulin (SHBG), indicate liver or thyroid dysfunctions. Thyroid hormones (TSH, fT3, fT4), T/E ratio and DHT levels should be evaluated in all impotent men.

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Table 3: Diagnostic approach to male sexual impotence

1. MEDICAL HYSTORY

- Medical: evaluation of risk factors and impotence associated diseases
- Sexual:

*rapid onset with normal early morning erections = psychogenic impotence

*progressive onset with impaired early morning erections = organic impotence

2. PHYSICAL EXAMINATION

- Body habitus (peripheric androgenization)
- Penile anatomy
- Testicular size and sensitivity
- Peripheric pulses
- Blood pressure

3. HORMONAL EVALUATION

- FSH, LH, PRL (0, +15, +30 minutes)
- Bio LH, Bio/Immuno LH ratio
- T, E, T/E ratio, FT, DHT
- TSH, fT3, fT4

4. VASCULAR EVALUATION

- ICI diagnostic procedure
- Basal and dinamic Duplex ultrasound
- Rigiscan evaluation after ICI
- Penile brachial index (PBI)

5. NEUROLOGIC EVALUATION

- Latency of bulbocavernous reflex
- Conduction velocity of the dorsal nerve of the penis
- Nocturnal Penile Tumescence (NPT)

3. Vascular evaluation:

ICI with prostaglandin-E_1 (PGE$_1$), combined with manual self-stimulation may be performed as the first diagnostic tool in all patients, to differentiate psychogenic from organic causes (Donatucci, Lue 1992). Usually, a positive ICI test implies normal veno-occlusive function, but may also occur during arterial dysfunctions (Pescatori et al, 1994). Thus cavernosometry / cavernosography are required in some patients. Sometimes ICI evaluation alone is not sufficient and a combination with the vacuum erection device (VED) can be a diagnostic tool for therapeutic approach (Lue 1994). Erectile failure in response to ICI has been described (von Heyden et al, 1993) and could be determined by an intrapenile discharge of vasoconstrictor mediators during the procedure (Kim, Oh 1992). Some selected subjects who do not respond to a maximal PGE$_1$ test-dose (20 mcg), may present high level of anxiety at the time of the ICI. In successive ICI sessions the addition of the α-1.2 blocker phentolamine (0.5 mg/ml) to PGE$_1$ may reduce to a minimum the presence of false negatives.

In order to rule out arterial abnormalities, penile arteries Duplex ultrasound under basal and pharmacostimulated conditions should be performed. Penile rigidity should be recorded manually or, preferentially, by a real time Rigiscan device (Meuleman et al, 1992). The Penile-Brachial-Index (PBI) is frequently used as an empiric method to evaluate arterial function, but its accuracy is low.

4. Neurologic evaluation:

Attention must be paid to: a) evaluation of penile cutaneous sensitivity, b) latency time of bulbocavernosus reflex, c) somatosensory evoked pudendal potentials, and d) conduction velocity of the dorsal nerve of the penis.

The use of the electromyogram (EMG) of the smooth muscles of the corpora cavernosa has been suggested for the diagnosis of autonomic neuropathies, but its use remains controversial (Berger et al, 1993). Assessment of nocturnal penile tumescence (NPT) with the Rigiscan device is useful to differentiate organic from psychogenic impotence. Spontaneous erections are detected during rapid eye movement (REM) sleep stages in normal men and in patients affected by psychogenic impotence but are absent in patients with organic impotence (Morales et al, 1990).

IV. Therapy

There are several options for the treatment of male erectile dysfunctions (Table 4).

A. Medical therapy:

Hormonal replacement therapy is suitable only in particular conditions, i.e. testosterone and its derivatives for androgen deficiency; and gonadotropins for hypogonadotropic hypogonadism. Bromocriptin is indicated for any dysfunctional hyperprolactinemia, while surgery is the treatment of choice when a pituitary adenoma is evident by instrumental investigations. Thyroid active drugs are prescribed when hypothyroidism (L-thyroxine) and hyperthyroidism (methimazole) are present, respectively.

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Table 4: Treatment options and appropriate agents used for male sexual impotence (ICI = intracavernous injection of vasoactive drugs; VED = vacuum eerection device;   PGE1- prostaglandin-E1;   PAPA = papaverine hydrochloryde; PHE = phentolamine mesylate; ATR = atropine sulphate; PO = per os; IC = intracavernous; IM = intramuscule; IN = intranasal; EOD = every other day; DDV = deep dorsal veins; DCV = deep cavernosal veins).

Type of impotence	Options	Appropriate Treatment	Dose
PSYCHOGENIC	Psychotherapy		
	VED		
	ICI	PGE1	
	Prostheses		2.5-10 mcg IC
NEUROGENIC	ICI	PGE1	2.5 - 20 mcg IC
	VED		
	Other medications	Trazodone	75-150 mg/day PO
		Yohimbine	20 mg / day PO
		L-arginine	2800 mg/ day PO
	Prostheses		
HORMONAL	Hormones	LH	5000 UI IM, weekly
		Testosterone	100 - 250 mg IM
		(enanthate/cypionate)	every 14 - 21. days
		Mesterolone	50 mg PO once a day
		Tamoxifen	20 mg PO once a day
		Bromocriptine	5-20 mg PO / day
		Naltrexone	50 mg PO EOD
		Gonadorelin	100 mcg IN six times a day
	Surgery (tumors)		
ARTERIAL	ICI	PGE1	20 mcg IC
	VED	Alone or + ICI	
	Other medications	Buflomedil. isoxsuprin, pentoxyfillne, etc.	Medical prescription
	Arterial surgery	Reconstruction, bypass	
	Prostheses		
CAVERNOSAL	ICI	PGE1+PHE+PAPA+ATR	1 ml= 10 mcg+1.01mg +12.1 mg+0.15mg IC
	VED	Alone or + ICI	
	Venous surgery	Ligation of DDV or DCV	
	Prostheses		

Encouraging results with GnRH pulsatile administration in patients with normal hormonal patterns are obtained, probably through a central action exerted from this hormone on the lymbic system (Isidori 1990).

Several vasoactive drugs may be helpful: α-2 adrenergic receptor blockers (i.e. yohimbine hydrochloryde). These potentiate the vasodilator action of parasympathetic nervous system. However, trials using oral medications containing yohimbine have failed to demonstrate a real improvement of erectile function (Susset et al, 1989). Trazodone is successfully used in some cases of impotence associated with psychological disturbances, due to it property to induce an α-adrenergic receptor blockade, thus interfering with the adrenergic control of penile detumescence, causing prolonged erections (Saenz de Tejada 1991). Clinical studies have indicated that apomorphine (a potent central dopamine agonist which acts by stimulating oxytocynergic neurons) plays a role in the treatment of erectile dysfunctions in men (Lal et al, 1987). Further investigations are in progress to determine its real efficacy. High oral doses of L-arginine (a nitric oxide precursor) may be helpful in some young impotent subjects not affected by venous incompetence (Zorgniotti 1994). Oral phentolamine may be effective in the clinical management of some selected patients (Zorgniotti 1994). In diabetics a tight control of blood glucose levels may avoid worsening of erectile dysfunction.

B. Intracavernous injection of vasoactive drugs (ICI):

The self-injection of vasoactive drugs (the most commonly used are papaverine, phentolamine, PGE$_1$ alone or in different combinations) directly in the corpora cavernosa induces smooth muscle relaxation and permits to achieve full erections (Virag et al, 1982; Virag, Adaikan 1987). Satisfactory results are obtained with vasoactive drugs combination also for severe veno-occlusive dysfunctions (Montorsi et al, 1993) (table 4). Caution and frequent medical specialistic controls are needed due to the high frequency of penile fibrosis and/or priapism.

C. Psychotherapy:

If NPT excludes an organic cause, psychosexual therapies (psychoanalytic treatment or cognitive-behavioral treatment) are indicated and may be highly helpful.

D. Vacuum erection device (VED)

The VED approved by the FDA in 1982, represents a noninvasive intervention which may be effective in producing an erection for men with organic, mixed and psychogenic etiologies (turner et al, 1990). VED should be used according to the patient's goal / desired treatment.

E. Surgery:

Semirigid or inflatable penile prostheses are indicated in patients who fail to respond to medical and ICI therapies. About 90% of patients report sexual satisfaction with penile prostheses, but neither ejaculation nor orgasm are allowed. Mechanical failure (10%) and

infections (5%) are the most common complications of prostheses implantation and frequent controls are required. Arterial reconstruction or bypass (arterial-corporeal, arterial-arterial and arteriovenous bypass) are exclusively indicated in patients with congenital or acquired arterial obstruction (i.e. pelvic or perineal traumas), inasmuch as different percentages of post-surgical failures have been described. The surgical treatment of veno-occlusive dysfunction (ligation of deep dorsal / cavernosal veins, excision of deep dorsal / cavernosal veins, transluminal venous ablation, suture ligation of emissary veins at tunica albuginea) remains controversial (Lue 1994).

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